



Food and Drug Administration
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November 25, 2015

IBL INTERNATIONAL GMBH
NICOLA KAISER
HEAD OF REGULATORY/ QM
FLUGHAFENSTRASSE 52 A
HAMBURG D-22335 GERMANY

Re: K150528

Trade/Device Name: Cortisol Saliva Luminescence Immunoassay
Regulation Number: 21 CFR 862.1205
Regulation Name: Cortisol (Hydrocortisone and Hydroxycorticosterone) Test System
Regulatory Class: II
Product Code: NHG
Dated: October 21, 2015
Received: October 22, 2015

Dear Nicola Kaiser:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>. Also, please note the regulation entitled, “Misbranding by reference to premarket notification” (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>.

Sincerely yours,


Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known)

k150528

Device Name

Cortisol Saliva Luminescence Immunoassay

Indications for Use (Describe)

The IBL International Cortisol Saliva Luminescence Immunoassay is intended for the in-vitro diagnostic quantitative determination of Cortisol in human saliva and for use as an aid in the diagnosis and treatment of adrenal disorders.

The device is not intended for point-of-care settings.

Type of Use (Select one or both, as applicable)

☒ Prescription Use (Part 21 CFR 801 Subpart D)

☐ Over-The-Counter Use (21 CFR 801 Subpart C)

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510(k) Summary k150528

For

Cortisol Saliva Luminescence Immunoassay

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3. Date Prepared

2015-11-24

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4. Device Name

Trade/Proprietary Name: Cortisol Saliva Luminescence Immunoassay
Common/Usual Name: Cortisol Saliva LUM

5. Classification Name

Classification Name: Enzyme Immunoassay, Cortisol, Salivary; Cortisol (hydrocortisone and hydroxycorticosterone) test system
Classification Regulation: 862.1205
Product Code: NHG

6. Predicate Device

Pantex INC. AM/PM Salivary cortisol EIA k102841.

7. Device Description**Summary and explanation:**

Cortisol (also known as hydrocortisone, compound F) is the main glucocorticoid in humans and is produced in the zona fasciculata of the adrenal cortex. 90 % of the circulating cortisol are bound to corticoid binding globulin (CBG, Transcortin), ca. 7 % are bound to albumin and only 1–3 % are unbound. Only the latter part represents the active form of cortisol. The free cortisol is released in saliva and is excreted via the kidneys as a small part among the metabolites of cortisol. The level of free cortisol in blood regulates mainly its secretion in the adrenal cortex in a negative feedback mechanism via CRH (corticotropin releasing hormone) in the hypothalamic region and the ACTH in the pituitary gland, but it is also affected by different situations above all by stress.

In humans, there is a physiological fluctuation of cortisol achieving the highest level in the morning and the lowest during the night. This fluctuation of cortisol plasma level is reflected in saliva normally with a peak in the first 90 minutes after waking up. The cortisol measurement is indicated in adrenal disorders. Due to the diurnal fluctuations of cortisol, a salivary sample collection is an easy method without the stress of repeated venipunctures.

Test principle:

Luminescence immunoassay based on the competition principle. An unknown amount of antigen present in the sample and a fixed amount of enzyme labelled antigen compete for the binding sites of the antibodies coated onto the wells. After incubation the wells are washed to stop the competition reaction. After addition of the luminescence substrate solution the intensity of the luminescence measured is inversely proportional to the amount of the antigen in the sample. Results of samples can be determined directly using the standard curve.

Device composition:

The device is available in two sizes, 96 tests and 960 tests.

The device consists of an antibody coated 96 well Microtiter Plate, seven Standards (range 0.015 - 3.20 µg/dL, equivalent to 0.15 - 32 ng/mL calibrated to the NIST cortisol), two Controls, Enzyme Conjugate (Cortisol coupled to peroxidase), Chemiluminescence Reagent 1 and 2, 10x concentrated Wash Buffer, Adhesive Foils.

8. Intended Use

The IBL International Cortisol Luminescence Immunoassay is intended for the in-vitro diagnostic quantitative determination of Cortisol in human saliva and for use as an aid in the diagnosis and treatment of adrenal disorders.

The device is not intended for point-of-care settings.

Technology Comparison

Item	Cortisol Saliva Luminescence Immunoassay	Enzyme Immunoassay, Cortisol Salivary
510(k) Number	K150528	K102841
Device name	Cortisol Saliva Luminescence Immunoassay	Enzyme Immunoassay, Cortisol Salivary
Analyte	Cortisol	Cortisol
Specimens	Saliva	Saliva
Method	Luminescence Immunoassay	Enzyme Immunoassay
Test principle	Luminescence immunoassay based on the competition principle. An unknown amount of analyte present in the sample and a fixed amount of enzyme labelled analyte competes for the binding sites of the antibodies coated onto the wells. After incubation the wells are washed to stop the competition reaction. After addition of the luminescence substrate solution the intensity of the luminescence measured is inversely proportional to the amount of the analyte in the sample. Results of samples can be determined directly using the standard curve.	The basis of the Cortisol Enzyme Immunoassay (EIA) is the quantitative relation between ligand concentration and the proportion of Cortisol (analog) enzyme conjugate bound to the antiserum. For example: Cortisol in the calibrators and unknowns compete with Cortisol coupled to peroxidase for antibody binding sites. After incubation, unbound components are washed away. The reaction between Cortisol peroxidase with the substrate (TMB) produces a blue color. The pre-determined time of incubation the reaction is stopped and a yellow color is formed. The optical density (read at 450 nm) is inversely proportional to the cortisol of calibrators, saliva samples and saliva controls.
Detection	RLU Measurement; luminescence	OD Measurement; OD microplate

Item	Cortisol Saliva Luminescence Immunoassay	Enzyme Immunoassay, Cortisol Salivary
	microplate reader	reader
Calculation	Quantitative	Quantitative
Quality control	Control low and high	Control low and high
Reportable range	0.012 µg/dL – 3.0 µg/dL	0.01 µg/dL – 3.0 µg/dL
Indications for use	The IBL International Cortisol Saliva Luminescence Immunoassay is intended for the in-vitro diagnostic quantitative determination of Cortisol in human saliva and for use as an aid in the diagnosis and treatment of adrenal disorders. The device is not intended for point-of-care settings.	For the in-vitro diagnostic quantitative determination of free and protein bound salivary cortisol in human saliva as an aid in the assessment of Cushing Syndrome and Addison's Disease. Measurements of cortisol in saliva are used on the diagnosis and treatment of disorders of adrenal gland.
Performance Characteristics		
Expected values (Normal range)	Ages: 21-70 AM: 0.079 - 1.290 µg/dL (N=157) PM: 0.042 - 0.436 µg/dL (N=168)	Ages 23-68 AM: 0.258 - 1.269 µg/dL (N=152) PM: 0.025 - 0.296 µg/dL (N=152)
Limit of Detection	Limit of Blank: 0.004 µg/dL	Limit of Blank: 0.00392 µg/dL.

Analytical Performance

Detection limits

The LoB study was conducted during three days of testing by one operator. The runs were performed with high and low kit controls and with five different samples. Each sample was tested five times in duplicate each run using two reagent lots.

The LoD/LoQ study was conducted during three days of testing by one operator. The runs were performed with high and low kit controls and with five different human saliva samples. Each sample was tested times in duplicate each run using two reagent lots.

Specificity

The cross reactivity study was conducted during eight days of testing by one operator. A maximum of five runs were performed per day with high and low kit controls and with three different human saliva samples spiked with potential interfering substance in six different concentrations(0, 0.1, 1, 10, 100, 1000 and 10000 µg/dL). Each sample was tested once in duplicate using one reagent lot.

Specificity of the IBL Cortisol Saliva LUM Assay test was assessed by testing a panel of 27 members. The cross-reactivity has been defined as:

$$\text{Cross-reactivity} = \frac{\text{concentration of cortisol at 50\% (B/B}_0\text{)}}{\text{concentration of cross reactant giving 50\% (B/B}_0\text{)}}$$

The use of topical creams or medication containing prednisolone and 11-Deoxycortisol should be avoided as they can cause preanalytical contamination of the saliva sample.

At $\geq 10\%$ Prednisolone is a potential interfering substance (from 10000 $\mu\text{g/dL}$).

At $\geq 5\%$ 11-Deoxycortisol is a potential interfering substance (from 10000 $\mu\text{g/dL}$).

Linearity

The linearity experiment was conducted according to the CLSI EP06-A during two days of testing by one operator. The runs were performed with high and low kit controls and with two different human saliva samples mixed up with each other to produce intermediate concentrations. Each sample was tested in duplicate using one reagent lot.

A linear correlation between the expected concentration and the determined concentration could be detected which showed the following best fit:

Determined Cortisol concentration ($\mu\text{g/dL}$) = $-0.05 + 1.03 \times (\text{expected Cortisol concentration } (\mu\text{g/dL}))$, with $R^2 = 0.99$.

The linear range of the assay is defined by the LoQ = 0.012 $\mu\text{g/dL}$ and the highest tested Cortisol concentration of 3.134 $\mu\text{g/dL}$ that showed an absence of a non-linear component.

Recovery

The Recovery study was conducted during one day of testing by one operator. The run was performed with high and low kit controls and with three different human saliva samples spiked with six different cortisol concentrations. Each sample was tested in duplicate using one reagent lot.

The recovery showed a minimum of 93.7% and a maximum of 109.6% for all tested samples and expected concentrations. The expected concentrations ranged from 0.242 $\mu\text{g/dL}$ to 2.528 $\mu\text{g/dL}$,

Precision

The Study was conducted during 1 day of pre-evaluation and familiarization period and 20 days of testing (based on CLSI Guideline EP05-A3). 6 assays were performed daily within a fully factorial design using 3 different reagent lots and 3 operators. Within each assay 7 human saliva pools were used and determined in triplicate

The between lot variation showed a CV range of 0.4 – 1.7% for the seven different concentrated human saliva samples.

The between operator variation showed a CV range of 0.8 – 1.8% for the seven different concentrated human saliva samples.

Interferences

Analytical Specificity

The analytical specificity study was conducted for every possible potentially substance during one day of testing by one operator. The runs were performed with high and low kit controls and with 3 different human saliva samples. Each sample was tested in duplicate using one reagent lot.

Sample Freezing Claim

The removal of the highly viscous components improves the pipetting precision. Freezing is believed to lead to the denaturation of the protein components of the viscous components. These denatured protein components were thereafter removed by centrifugation of the sample.

The mean of the coefficient of variation for freezing was lower than the mean of the coefficient of variation for samples that have not been frozen once (Mean CV = 4.4% after freezing vs. 7.2% without freezing process).

In addition the stability of Cortisol in samples was evaluated. Five samples for which the Cortisol concentration is known (low, medium and high concentration) and an acceptance range had been established were stored at the following conditions:

1. $\leq -20^{\circ}\text{C}$ for 3, 6 and 12 months
2. $2-8^{\circ}\text{C}$ for 1, 2 and 4 weeks
3. $19-26^{\circ}\text{C}$ (RT = room temperature) for 1, 2 and 4 weeks
4. $36-39^{\circ}\text{C}$ for 4 days, 1 week and 2 weeks
5. 50°C for 1 day, 4 days and 1 week.

Within all samples stored at the above conditions, the concentration of Cortisol was determined within the predetermined acceptance range. The sample stability is listed in the following table:

Storage	37°C	18-25°C	2-8°C	$\leq -15^{\circ}\text{C}$
Stability	1 week	2 weeks	2 weeks	6 months

Microtiterplate Humidity

The effect of humidity and temperature on the coated wells was evaluated by storing the microtiter strips at three different grades of humidity (dry, ambient and wet saturated) and three different temperatures (2-8°C, 19-26°C and 35-39°C) for 7 days, 14 days and 4 weeks. No loss in functionality of the IBL Cortisol Saliva LUM was observed following the different treatments and these treatments did contain the worst case scenario that the IBL Cortisol Saliva LUM might be subjected to.

Real-time Stability

The assay shows full functionality and is stable for at least 34 months at 2°C-8°C. The kit stability includes a safety margin anticipating the use of the kit beyond the stated expiration date by the customer. This safety margin has been set to 6 months. Even if the 34 months stability results demonstrate full functionality of the IBL Cortisol Saliva LUM, the stability claim on the kit however only states a maximal shelf life of 18 months in order to increase safety and effectiveness of the device.

Traceability

The cortisol results obtained with the IBL Cortisol Saliva LUM are metrological traceable to the SI-Unit µg/dL by the cortisol concentration of the standard reference material (Ref. 921) provided by the National Institute of Standards and Technology (NIST).

The assigned standard concentrations were confirmed by comparison to NIST Cortisol reference material with following linear regression analysis:
 $y = 0.9852x + 0.006$, $R^2 = 0.999$ and with a mean uncertainty of 2 %.

Reference Interval Study

Reference intervals were established using prospectively 325 collected samples from apparently healthy 76 males and 76 females at two independent time points at one collection site located within the United States.

Saliva was collected using the Cortisol Salivette from SARSTEDT Int. (FDA listing number: D053653). The inclusion criteria for the healthy adult population was adults between 21-70 years of age, genders and race with normal TSH and TPO levels, were not currently undergoing medical treatment or drug therapy, and were free of illness on the day of sample collection.

The exclusion criteria included patients on cortisol therapy, on hormone therapy or taking oral contraceptives, patients with implanted contraceptive

devices, history of thyroid or other autoimmune disease, history of Cushing's syndrome or Addison's disease, pregnant or lactating women.

The reference interval study was conducted during five days of testing by two different operators. A maximum of three runs were performed per day with high and low kit controls and with the different human saliva samples. Each sample was tested once in duplicate using one reagent lot.

Clinical Testing

The design, development and testing of the Cortisol Saliva Luminescence Immunoassay device has not resulted in the need for any clinical trials.

The laboratory clinical testing that was performed is listed above. These were performed in the laboratory with no human clinical trials being performed.

Non-Clinical Testing

The laboratory testing for clinical evaluation was performed using IBL International's Cortisol Saliva Luminescence Immunoassay (Cortisol Saliva LUM) versus Pantex INC. AM/PM Salivary cortisol EIA (k102841) predicate device. Laboratory data were presented to evaluate clinical accuracy of results. The performance characteristics of the Cortisol Saliva Luminescence Immunoassay were verified by several studies as LOB-LOD-LOQ, specificity, linearity, recovery, stability, precision, patient preparation claim, sample freezing claim, MTP humidity, analytical specificity, method comparison and reference interval. Testing results indicate that the Cortisol Saliva Luminescence Immunoassay perform satisfactorily when used appropriately, as outlined in the package insert.

Method Comparison Study

The Method comparison study was conducted during five days of testing by one operator. The runs were performed with high and low kit controls and with the different human saliva samples. Each sample was tested in duplicate using one reagent lot.

A comparison of the IBL Cortisol Saliva LUM and the predicate device was completed. The results of weighted deming regression of Cortisol concentrations measured with the IBL LUM (y) and with the comparison methods (x) in human saliva samples are summarized in the following table. Pantex AM/PM Salivary Cortisol Enzyme Immunoassay (K102841) (abbreviated: Pantex Salivary Cortisol EIA). This comparator assay is cleared up to 3.0 µg/dL.

The results of the method comparison are described by the weighted deming regression:

Y – Test Unit	X – Comparison Unit	N	R	y = a +bx
IBL	Pantex Salivary Cortisol EIA	169	0.993	y = -0.017 + 0.902x

Weighted deming regression for the Cortisol Saliva LUM versus the predicate device show very strong correlation. Therefore the IBL Cortisol Saliva LUM is demonstrated to be accurate up to 3.0 µg/dL, and is assumed to be substantially equivalent to the additional comparator of the 510k cleared device of Pantex Salivary Cortisol EIA.

Reportable range in the instructions for Use is stated as 0.012 – 3.0 µg/dL.

Conclusion

Laboratory study results indicate that the intended users were able to obtain comparable testing data when using the Cortisol Saliva Luminescence Immunoassay and the legally marketed predicate devices.

The testing results supports that all the product specifications have met the acceptance criteria as completed during the laboratory testing. The device hazard analysis was completed and risk control implemented to mitigate identified hazards. The Cortisol Saliva Luminescence Immunoassay device passed all testing and supports the claims of substantial equivalence to the predicate device.

The Cortisol Saliva Luminescence Immunoassay device has the same intended use and technological characteristics as the predicate devices.